

Notice of Allowability

Application No.

10/725,277

Examiner

Anthony J. Paviglianiti

Applicant(s)

TANG ET AL.

Art Unit

1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to Applicant's Amendment to Claims dated 6/3/2005.
2. ☒ The allowed claim(s) is/are 1-7.
3. ☐ The drawings filed on _____ are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
 6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08),
Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413),
Paper No./Mail Date _____
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____

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DETAILED ACTION

Claims 1 – 7 are currently pending in the application. Applicant's "Amendments to the Claims," dated June 3, 2005, were received and are hereby acknowledged. **Claims 1, 2, 3 and 5** were amended by Applicant. No new matter was found.

Priority

This application is a division of Application No. 09/871,700, filed on June 4, 2001, and which became U.S. Patent 6,706,709. This application claims benefit of U.S. Provisional Application 60/209,162, filed June 2, 2000.

Response to Amendment

Applicant's "remarks" accompanying the Amendment to the Claims, dated June 3, 2005, are hereby acknowledged. The following sections address each of the rejections and objections made in the first Office Action dated February 28, 2005.

Double Patenting

In the first Office Action, **Claims 1 – 6** of the present application were rejected on the basis of double patenting with U.S. Patent No. 6,506,763 and (provisional) double patenting with co-pending U.S. Patent Application 10/736,243 [now U.S. Patent No. 6,861,418].

Applicant has overcome the examiner's rejection by submitting a Terminal Disclaimer as to U.S. Patent No. 6,506,763 and U.S. Patent No. 6,861,418 [formerly U.S. Patent Application No. 10/736,243] which was approved by the Office on June 14, 2005.

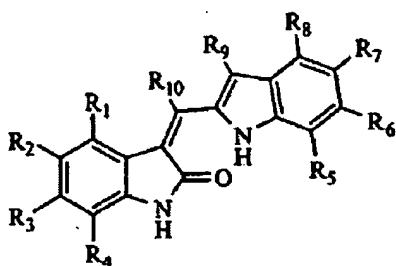
Claim Objections:

Applicant has obviated the Claim Objections to **Claims 2(b), 3(b), 3(c), 5(b) and 5(c)**, by amending "halo" to "halogen" in **Claims 2, 3 and 5** to be consistent with "halogen" in **Claim 1**.

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Restriction Requirement:

Applicant's election, with traverse, of the chemical compound "5-bromo-3-[5-(2-morpholin-4-yl-ethoxy)-1H-indol-2-ylmethylene]-1,3-dihydro-indol-2-one" ("IN-008" in Table 1; also, Claim 7, example 8) in his Remarks dated June 3, 2005, is respectfully acknowledged. There had been no restriction requirement among inventions, as all of the pending claims in this Divisional application (Claims 1 – 7) were drawn to compounds of formula (I),



, as depicted in **Claim 1**. As described in the first Office Action, the search of the prior art was expanded beyond the elected compound to encompass all related compounds having this core structure of formula (I) where substituent **R₇** is: alkyl- or alkoxy-*morpholinyl* groups (as in the elected compound), as classified in Class 544, subclass 144; and expanded further to encompass alkyl- or alkoxy-*pyrrolidinyl* groups or alkyl- or alkoxy-*diethylamino* substituents, as classified in Class 548, subclass 455 (see Office Action, page 14, lines 1 – 4); as well as each of the forty-two chemical compounds listed in the independent claim, **Claim 7**.

Response to traverse of restriction requirement:

In the written response, Applicant traversed the examiner's requirement for election of a single chemical species on the grounds that all of the compounds in the original claims had the same indolinone core structure and would therefore pose no undue burden on the examiner to search the entire breadth of claims as originally presented. Upon reconsideration of the

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restriction requirement for the election of a single compound of the invention for examination purposes, the examiner states that the "indolinone" core cited by applicant is known in the prior art (see, for example, those indolinone compounds cited as closest prior art in the first Office Action), and therefore it would be the scope of its substituents, $R_1 - R_{10}$, that would determine the size of the relevant art to be searched. As claimed in this application, R_1 , R_2 , R_3 and R_7 , when given their broadest reasonable range of values in light of the disclosure, would encompass a vast number of compounds which would be classified within numerous subclasses of Classes 540, 544, 546, and 548, such that a complete search of the relevant art would not be possible (for example, R_2 and R_3 could be any optionally-substituted heteroaryl, and R_7 could be any alkyl or alkoxy group substituted with any heteroaliphatic ring). As originally presented, the substituents $R_1 - R_{10}$ on the indolinone core encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. §103 with respect to the other member. For example, a compound of formula (I) substituted on the indolinone ring at the 5-position (i.e., R_7) position with a "methyl-piperazinyl group" would not anticipate or render obvious another compound of formula (I) substituted at R_7 with a "pentyl-oxazolidine" group. Taken as a whole, and after reconsideration of these factors, the examiner believes that the requirement to elect a single chemical compound for the examination of the case was appropriate and therefore the requirement for election of a single compound for purposes of the examination is maintained.

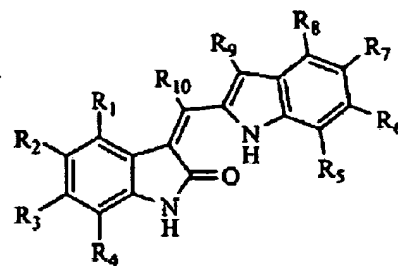
As a practical matter, during the course of the examination, the examiner expanded the search of the art beyond the elected compound to all related compounds within its same

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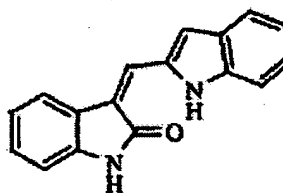
classification group, and further expanded the search to encompass compounds within an additional classification group which was the most frequently-represented among the forty-two individual chemical compounds claimed in **Claim 7**.

Reasons for Allowance

The following is the examiner's statement for reasons for allowance: The present



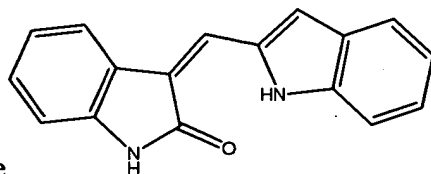
invention is directed to indolinone compounds of formula (I), as depicted in **Claim 1** (as amended), where substituent **R₇** is selected from the group consisting of a lower alkyl substituted with a morpholinyl ring or pyrrolidinyl ring or dialkylamino group and lower alkoxy substituted with a morpholinyl ring or pyrrolidinyl ring or dialkylamino group. The present invention is also directed to forty-two individual chemical compounds listed in an independent claim, **Claim 7**.



Although the core indolinone structure, is known in the art (see examples below), the compounds of the present invention were free of the prior art because of the novelty conferred by the substituents (as amended) at the 5-position (i.e., **R₇**) on the indolinone core of formula (I).

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The closest prior art was disclosed in an article by Dr. Cinzia Lanzi of a compound with



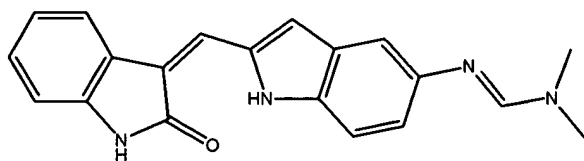
the structure

, which anticipates all of the limitations of **Claim 1**

in the present invention except for the requisite substituent at the “5” position (i.e., **R₇**) on the indolyl ring (“substituted alkyl [or] substituted alkoxy”). See C. Lanzi, “Inhibition of Transforming Activity of the ret/ptc1 Oncoprotein by a 2-Indolinone Derivative,” *Int. J. Cancer*, vol. 85, pages 384 – 390 (published online January 28, 2000), especially Compound 7 in Figure 1, on page 385 and page 384, 2nd col., lines 19 – 20. The Lanzi compound, like those compounds in the present invention, had biological activity as an inhibitor of protein kinases. *Id.* at p. 384, lines 15 – 20. However, the Lanzi reference did not teach any compounds with substituents at the “5” position of the indolyl ring, and therefore does not anticipate or render obvious the compounds of the present invention in **Claims 1 – 7**, as amended.

Another closely-related compound was disclosed in **U.S. Patent No. 4,642,309**, by H. Michel, et al., which discloses a compound wherein 2-indolinone is linked to a 2-indolyl group via a methylene chain, but, like the Lanzi compound above, has no substituent at the “5” position of the 2-indolyl group and therefore does not anticipate or render obvious the compounds of the present invention.

Similarly, **U.S. Patent No. 5,849,710**, by Carlo Battistini, et al., discloses a compound of



structure

, which, unlike other close prior art cited

in this section, has an “aminomethylene-*N,N*-dimethylamino” substituent group at the “5-

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position" (i.e., **R₇**) of the indole ring. However, the claims of the present invention, as amended, require **R₇** to be "selected from the group consisting of a lower alkyl substituted with a morpholinyl ring or pyrrolidinyl ring or dialkylamino and lower alkoxy substituted with a morpholinyl ring or pyrrolidinyl ring or dialkylamino," which is not disclosed in **U.S. Patent No. 5,849,710**. In addition, none of the forty-two chemical compounds claimed in **Claim 7** are attached via a nitrogen atom at the 5-position of the indole core; therefore, the Battistini reference does not anticipate or render obvious the compounds of the present invention.

In addition, **U.S. Patent No. 6,531,502** (first published as WO 00/08202 on Feb. 17, 2000) by Tang, et al., as well as a journal article by **H. von Dobeneck** in Chemische Berichte, vol. 102(4), pages 1347-56 (1969) (compound 19 on page 1351), both disclose a compound where 2-indolinone is linked to a 2-indolyl group via a methylene chain, but each has substituents at the "3" position of the indolyl group (dimethylpropyl and methyl groups, respectively) rather than at the requisite "5" position ("**R₇**"). Neither one of these two references teaches that the substituent groups may be placed at the "5" position on the indolyl group, and therefore neither source anticipates or renders obvious the compounds of the present invention.

Therefore, based on the analysis above, **Claims 1 – 7, as amended by Applicant in the "Amendments to the Claims" dated June 3, 2005**, are not anticipated or rendered obvious by the prior art of record, and **are allowable**.

Any comments considered necessary by Applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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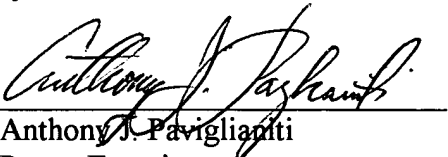
Conclusion

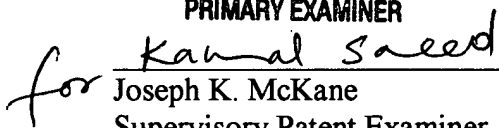
Claims 1 – 7, as amended by Applicant's "Amendments to the Claims" dated June 3, 2005, are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Anthony J. Paviglianiti** whose telephone number is **(571) 272-3107**. The examiner can normally be reached on Monday-Friday, 8:30 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached at (571) 272-0699. **The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Please note that this is a new central FAX number for all official correspondence.**

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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